

**The efficacy and safety of faster insulin aspart (Fiasp) compared to conventional insulin aspart as correction bolus in patients with type 1 diabetes using continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM): a cross-over controlled trial**

INVESTIGATOR-INITIATED STUDY PROPOSAL

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**Background and significance:**

Patients with type 1 DM using CSII require bolus insulin for two purposes: first, to cover carbohydrate intake to control postprandial glucose, and second, to correct episodes of hyperglycemia. The latter function is referred to as a “correction dose” or “correction bolus”. Insulin pumps have bolus calculators which calculate correction doses based on the patient’s individualized BG target and insulin sensitivity factor (ISF). Rapid-acting insulin analogues delivered by pump typically require 2 to 4 hours to fully correct an acute hyperglycemic episode, and sometimes multiple correction doses are needed to normalize the blood glucose level. This can be frustrating for patients, particularly when a correction bolus is necessary in addition to a meal bolus; frequently, patients must wait for the correction bolus to take effect and delay eating until the blood glucose has begun to normalize to avoid severe postprandial hyperglycemia. There is consequently an unmet need in insulin delivery, and in particular in CSII, for an insulin which can correct a hyperglycemic episode more rapidly than is currently possible with rapid-acting insulin analogues.

Faster insulin aspart (Fiasp) is a novel formulation of insulin aspart with an accelerated time-action profile which results in twice the exposure to insulin and 74% greater insulin action within the first 30 minutes after injection compared to conventional insulin aspart (1). This results in twice-as-fast onset of appearance in the bloodstream (4 vs. 9 min compared to conventional insulin aspart) (1) which has been demonstrated to reduce postprandial glucose levels in patients with type 1 DM using CSII (2, 3). Theoretically, this faster insulin action would be useful in correction dosing during acute episodes of hyperglycemia to normalize the blood glucose level more rapidly than is currently possible with conventional insulin aspart (NovoLog).

Many patients with type 1 DM using CSII now also use continuous glucose monitoring (CGM) for making insulin dosing decisions. Currently the FDA has approved 2 CGM systems for nonadjunctive use in bolus insulin dose calculations. Only one of these systems, the Dexcom, reads continuously to the patient and has alarms to warn of impending episodes of hyper- or hypoglycemia, and this is the system used most commonly by patients with type 1 DM using open-loop CSII. Patients now incorporate the Dexcom trend arrow, which depicts the rate and direction of glucose change, into the correction dose calculation, and recommendations on how to incorporate CGM information into correction dose calculations have recently been updated based on an expert consensus report (4). However, these guidelines were created for use with rapid acting insulin analogues. How they might need to be modified for use with Fiasp (the first and only ultra-rapid insulin analogue) is not known.

The purpose of this investigator-initiated trial is to compare the efficacy in terms of time to recovery from hyperglycemia as measured by time to arrest of hyperglycemic excursion ("glucose plateau point", primary endpoint) and return to premeal glucose target if feasible (secondary endpoint) between Fiasp and conventional insulin aspart when used as a correction bolus. These endpoints will be determined by CGM (Dexcom) from data exported from the Dexcom Clarity program.

## **SPECIFIC OBJECTIVES**

Primary objective:

To compare time to stabilization of rising blood glucose level after correction bolus between Fiasp and NovoLog. This data point will be referenced to as the "glucose plateau point" (GPP). The time of each correction bolus will be captured from the pump download, and correlated with Dexcom Clarity reports to identify the GPP.

The time to return to premeal target glucose after use of a correction bolus, if feasible,\* to achievement of pre-meal target glucose, which will be individualized per subject (though most subjects will have a glucose target of 100 mg/dL).

\*This parameter will be analyzed for correction boluses which were isolated and the subject did not consume additional carbohydrate until after he/she returned to the premeal target.

Secondary objectives:

1. Incidence of early post-correction hypoglycemia (within 60 minutes and 120 minutes of use of correction bolus) with each insulin (key safety endpoint) (5,6).
2. To quantify the difference between insulin sensitivity factor (ISF) and insulin-on-board (IOB) time, if any, for correction dosing between NovoLog and Fiasp.
3. Percent time in target range 70-180 mg/dL by CGM for each insulin bolus.
4. Percent time in hyperglycemic range by CGM for each insulin bolus. Hyperglycemia ranges to be captured will include Category 1: 181-250 mg/dL and Category 2: above 250 mg/dL.
5. Percent time in hypoglycemic range below 70 mg/dL by CGM for each insulin bolus. Hypoglycemia ranges to be captured include Category 1: 69-54 mg/dL and Category 2: below 54 mg/dL.

6. GlycoMark (1,5 anhydroglucitol, a marker of postprandial glucose excursion) during use of each insulin.
7. HbA1c during use of each insulin.

## RESEARCH DESIGN AND METHODS

### Study hypothesis:

Compared to conventional insulin aspart, Fiasp will correct hyperglycemia (defined as arrest of rise of blood glucose, following correction bolus, ie, GPP ) faster than conventional insulin aspart in subjects with type 1 DM using CSII.

## ENDPOINTS

### Primary endpoint:

Time (in minutes) to stabilization of rising BG (GPP) by CGM after correction bolus during the final 2 week maintenance period. Two categories of correction dose will be analyzed: 1) those following an isolated correction dose (taken independently of a meal dose), and 2) those taken as part of a combination bolus with a meal dose.

### Secondary endpoints:

1. Incidence of early hypoglycemia (BG < 54 mg/dl within 1 and 2 hours) following correction bolus with each insulin (key safety endpoint).
2. Change in ISF, if any, required for hypoglycemia prevention using Fiasp and quantification of same.
3. Change in IOB, if any, required for prevention of late hyperglycemia using Fiasp and quantification of same.
4. GlycoMark (1,5 anhydroglucitol, a measure of postprandial glucose excursion) on each insulin.
5. HbA1c on each insulin.
6. Percent time spent in target range, hyperglycemic range and hypoglycemic range by CGM on each insulin during the final 2 weeks of each treatment period.
7. Standard deviation of mean blood glucose as determined by CGM on each insulin.
8. Treatment related impact measures on each insulin (TRIM D questionnaire).

Study endpoints will be obtained from each subject's CGM and insulin pump data during the final 2 weeks of each treatment period.

## STUDY TYPE

This is a 25-week open-label prospective single center 2 arm crossover trial.

## STUDY POPULATION

45 subjects with type 1 diabetes with good glycemic control who are experienced in the use of CSII (with any open loop pump) and CGM (Dexcom) will be randomized either to use Fiasp or conventional insulin

aspart in CSII. The study population will be derived from established clinic patients at Mountain Diabetes and Endocrine Center.

#### **INCLUSION CRITERIA**

1. Male and female patients  $\geq 18$  years of age
2. Type 1 DM of  $> 1$  year duration
3. Use of any open loop insulin pump, Tandem T-Slim with Basal IQ, Insulet Omnipod Dash, or any other investigator-approved insulin pumps with Dexcom CGM G5, G6, or newer version for  $> 6$  months
4. Good baseline glycemic control ( $HbA1c \leq 7.5\%$ ; low risk of hypoglycemia by CGM as defined by Dexcom Clarity report)
5. No episodes of severe hypoglycemia in the previous 3 months
6. Pump download shows regular meal bolusing, accurate carbohydrate counting ability, and willingness to use exercise markers in Dexcom
7. CGM download shows regular use ( $>85\%$  of time) and regular calibration if using G5 sensor (G6 requires no calibration)
8. Females using adequate contraception

#### **EXCLUSION CRITERIA**

1. Use of CGM other than Dexcom G5 or G6 or a newer Dexcom CGM version
2. Suboptimal baseline glycemic control ( $HbA1c > 7.5\%$ )
3. Pump or CGM download shows suboptimal use of devices (lack of meal boluses, frequent overrides of pump, excessive pump suspension, inadequate calibration or inconsistent usage of CGM)
4. Serious comorbidities including CVD with recent event, actively treated malignancy, renal dysfunction with  $eGFR < 45$  ml/min, or any other condition which in the opinion of the investigator would preclude subject's ability to participate in trial
5. Females unwilling to use contraception, planning pregnancy or breastfeeding
6. Use of any other glucose-lowering agents than insulin
7. Hypersensitivity to insulin aspart or one of the excipients in faster insulin aspart
8. Known diabetic gastroparesis

#### **WITHDRAWAL CRITERIA**

Females who become pregnant will be withdrawn from the study. Any subject may withdraw consent at any time.

#### **SUBJECT REPLACEMENT**

Subjects withdrawn from the study prior to randomization will be replaced; subjects withdrawn after randomization will not be replaced.

#### **RATIONALE FOR STUDY POPULATION**

Only subjects with good baseline glycemic control who are experienced in optimal use of CSII and CGM will be eligible for this study. This will minimize the effect of incorrect device usage (omission of meal boluses or inaccurate assessment of meal boluses, excessive overrides of the pump's bolus recommendations, excessive time disconnected from the pump, inconsistent CGM use, etc) as a confounding factor in the assessment of each insulin's efficacy. In other words, these patients have already optimized diabetes self-management and device usage; any change in glycemic control can therefore be attributed to the difference in pharmacologic profile of the insulin, not to patient behavior.

## VISIT PROCEDURES

### Overview:

45 subjects with type 1 diabetes with good glycemic control who are experienced in the use of CSII (with any open loop pump) and CGM (Dexcom G5 or G6) will be randomized either to use Fiasp or conventional insulin aspart in CSII. CSII settings (basal, bolus, and correction factors) will be optimized for a 2-week run in period followed by a 10-week period of CSII use with the assigned insulin. After a 12-week maintenance period, each group will cross over to the other insulin (conventional insulin aspart or Fiasp) by CSII for a second 2-week optimization period followed by a 10-week treatment period. Subjects will be instructed to enter the premeal interstitial BG (IBG) into the pump as per standard practice (for calculation of the correction insulin bolus) and the 1 and 2-hour postprandial IBG following each meal which will be captured by Dexcom. The time to flattening of the BG (GPP) will be captured from the raw data report exported from Dexcom Clarity. The time required from initiation of the correction bolus to GPP and from time of correction bolus to premeal target IBG (if feasible) will be captured for each insulin. Hypoglycemic events and their timing, in particular in relation to insulin boluses, will also be captured.

### Meal Challenge:

Meal challenge protocol to determine Insulin Sensitivity Factor (ISF) (also called Correction Factor (CF)), time to GPP, and time to correction of hyperglycemic excursion by CGM

At the randomization visit and at the insulin crossover visit (Visits 2 and 8), each subject will perform a meal challenge to assess the time GPP and to return to premeal glucose target using a Correction Bolus (CB) after induction of hyperglycemia following a carbohydrate load from a standard liquid meal (consisting of 8 oz Ensure: 32 grams CHO, 9 gm protein, 6 mg fat). This visit may require up to 5 hours of observation. The ISF will be customized for each insulin based on the decline of BG from post-Ensure peak BG to nadir to prevent future post-correction hypoglycemia.

### Protocol:

1. At Visit 2, subject will be randomized to Novolog or Fiasp. At Visit 8, the subject will cross-over to the other study insulin from Visit 2.
2. Prior to randomization or crossover and completion of each meal test, the subject's blood glucose must be  $\leq 150$  mg/dL. If the subject's blood glucose is greater than 150 mg/dL, the visit will be rescheduled.

3. On site at Visits 2 and 8, the subject will change infusion site and cartridge and fill the cartridge with the designated insulin. The new site and cartridge will be placed prior to the meal challenge so that the designated insulin is used for the meal challenge.
4. Subject will ingest an 8 oz bottle of Ensure, consuming the meal within 5 minutes, without a meal bolus. Subject will have a calibrated Dexcom sensor in place.
5. The time to peak post-Ensure hyperglycemic response and the magnitude of hyperglycemia will be recorded.
6. At the time of peak response (flattening of Dexcom trend arrow at highest BG level), a correction bolus (calculated using subject's usual BG target and Insulin Sensitivity Factor (ISF)) will be administered in the usual fashion via insulin pump.
7. The time to achievement of the GPP (flattening of the glucose trend arrow) and return to premeal target BG for each insulin will be documented.
8. The Dexcom display will be observed for 2 to 3 hours post correction bolus. If the subject experiences a BG below 70 mg/dl in that time, the ISF will be modified (increased by 15 to 20%) to prevent post-correction hypoglycemia.

## STUDY VISIT PROCEDURES

**Visit 1 (Screening Visit), Week -1:** Obtain written informed consent; review inclusion/exclusion criteria; demography (including child bearing potential and tobacco use); medical history; record concomitant medications; vital signs (including height, weight and BMI); diabetes history, pump and Dexcom downloads; insulin pump settings adjustments (if needed). Provide and educate subject about diaries; review Rule of 15 treatment for hypoglycemia (consume 15 grams of carbohydrate/re-check BG in 15 minutes) and hypoglycemia assessment; confirmation of consumption of 3 meals daily; collect venous sample for HbA1c and GlycoMark (LabCorp); subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion; review of infusion site reactions and occlusions; perform urine pregnancy test, if applicable; dispensing of trial product

**Visit 2: (Randomization Visit) Week 0:** office visit; vital signs; physical exam; subject attends visit fasting; completion of Meal Challenge. Randomize subject per protocol. Placement of new infusion site with conventional insulin aspart or Fiasp as per randomization. Subject completes TRIM D questionnaire. Device downloads; insulin optimization/titration; insulin pump settings adjustments including ISF/CF (if needed); subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion; assessment of infusion site reactions and occlusions; troubleshooting; assessment of AEs and concomitant medications; review and dispensing of diary; dispensing of trial product; technical complaints; review Rule of 15 for hypoglycemia and hypoglycemia assessment; confirmation of consumption of 3 meals daily; instruction in designated insulin use

**Visit 3, Week 2:** office visit; vital signs; device downloads; insulin optimization/titration; insulin pump settings adjustments (if needed); assessment of infusion site reactions and occlusions; troubleshooting; confirmation of consumption of 3 meals daily; assessment of AEs and concomitant medications; review and dispensing of diary; dispensing of trial product; technical complaints; drug accountability; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 4, Week 4:** phone visit; online Dexcom device download with review; adjust pump settings if needed; assess AE's and concomitant medications; review diary; confirmation of consumption of 3 meals daily; technical complaints; assessment of infusion site reactions and occlusions; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 5, Week 6:** office visit; vital signs; device downloads; insulin optimization/titration; insulin pump settings adjustments (if needed); assessment of infusion site reactions and occlusions; troubleshooting; confirmation of consumption of 3 meals daily; assessment of AEs and concomitant medications; review and dispensing of diary; dispensing of trial product; dispense Dexcom CGM sensor; technical complaints; drug accountability; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 6, Week 8:** phone visit; online Dexcom device download with review; adjust pump settings if needed; assess AE's and concomitant medications; review diary; confirmation of consumption of 3 meals daily; technical complaints; train subject how to enter bolus information into Dexcom history, assessment of infusion site reactions and occlusions; review Rule of 15 for hypoglycemia and hypoglycemia assessment; Subjects will be instructed to take entire correction dose at once and do not repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose 2. Suspected set occlusion

**Visit 7, Week 10:** phone visit; online Dexcom device download with review; adjust pump settings if needed; assess AE's and concomitant medications; review diary; confirmation of consumption of 3 meals daily; technical complaints; re-educate subject how to enter bolus information into Dexcom history; assessment of infusion site reactions and occlusions; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 8 (Treatment Crossover Visit), Week 12:** office visit; vital signs; physical exam; subject attends visit fasting; completion of Meal Challenge. Placement of new infusion site with the conventional insulin aspart or Fiasp as per crossover. Subject completes TRIM D questionnaire. Device downloads; insulin optimization/titration; insulin pump settings adjustments including ISF/CF (if needed); assessment of infusion site reactions and occlusions; troubleshooting; assessment of AEs and concomitant medications; review and dispensing of diary; dispensing of trial product; technical complaints; review Rule of 15 for hypoglycemia and hypoglycemia assessment; confirmation of consumption of 3 meals daily; instruction in designated insulin use; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion; collect venous sample for HbA1c and GlycoMark (LabCorp); perform urine pregnancy test, if applicable

**Visit 9, Week 14:** office visit; vital signs; device downloads; insulin optimization/titration; insulin pump settings adjustments (if needed); assessment of infusion site reactions and occlusions; troubleshooting; confirmation of consumption of 3 meals daily; assessment of AEs and concomitant medications; review and dispensing of diary; dispensing of trial product; technical complaints; drug accountability; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 10, Week 16:** phone visit; online Dexcom device download with review; adjust pump settings if needed; assess AE's and concomitant medications; review diary; confirmation of consumption of 3 meals daily; technical complaints; assessment of infusion site reactions and occlusions; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 11, Week 18:** office visit; vital signs; device downloads; insulin optimization/titration; insulin pump settings adjustments (if needed); assessment of infusion site reactions and occlusions; troubleshooting; confirmation of consumption of 3 meals daily; assessment of AEs and concomitant medications; review and dispensing of diary; dispensing of trial product; dispense Dexcom CGM sensor; technical complaints; drug accountability; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 12, Week 20:** phone visit; online Dexcom device download with review; adjust pump settings if needed; assess AEs and concomitant medications; review diary; confirmation of consumption of 3 meals daily; technical complaints; train subject how to enter bolus information into Dexcom history; assessment of infusion site reactions and occlusions; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 13, Week 22:** phone visit; online Dexcom device download with review; adjust pump settings if needed; assess AE's and concomitant medications; review diary; confirmation of consumption of 3 meals daily; technical complaints; re-educate subject how to enter bolus information into Dexcom history; assessment of infusion site reactions and occlusions; review Rule of 15 for hypoglycemia and hypoglycemia assessment; subjects will be instructed to take entire correction dose at once and not to repeat correction dose unless 1. No flattening of trend arrow by 2 hours after correction dose or 2. Suspected set occlusion

**Visit 14 (End of Study Visit), Week 24:** office visit; vital signs; physical exam; Placement of new infusion site with post-trial insulin; Subject completes TRIM D questionnaire. Device downloads; insulin pump settings adjustments including ISF/CF (if needed); assessment of infusion site reactions and occlusions; troubleshooting; assessment of AEs and concomitant medications; review of diary; drug accountability; technical complaints; review Rule of 15 for hypoglycemia and hypoglycemia assessment; instruction in designated insulin use; collect venous sample for HbA1c and GlycoMark (LabCorp); perform urine pregnancy test, if applicable

## **ASSESSMENTS OF EFFICACY**

These will include the time in minutes as captured by CGM (Dexcom) to arrest of rise in BG (GPP) after use of correction dose (primary endpoint); other CGM (secondary) endpoints will include: time to return to premeal target blood glucose if feasible, percent time in target range, hyperglycemia, hypoglycemia and SD by CGM, HbA1c and GlycoMark (LabCorp assay; Burlington, NC).

## **ASSESSMENTS OF SAFETY**

The key safety endpoint will be capturing the frequency and timing of hypoglycemic events, defined as BG < 54 mg/dl by CGM or by glucose meter or any BG measured by CGM or glucose meter requiring



assistance for treatment. If a CGM hypoglycemic event is verified by fingerstick BG and the meter and CGM BG values are discordant, the meter BG will be considered the accurate reading only for Dexcom G5.

The reference document, local (US) Prescribing Information, will be used for evaluation of expectedness of Adverse Events. All adverse events resulting from incorrect storage or usage of study product as per product labelling, if applicable, will be reported to the appropriate institutions (Reference ID:4160518). The investigator will copy Novo Nordisk when expediting SAE information to health authorities and will report all SAEs related to Novo Nordisk products to the local Novo Nordisk affiliate safety department. SAE submission to Novo Nordisk will be within 15 days from the investigator's first awareness of the event.

### **ASSESSMENTS OF SUBJECT COMPLIANCE**

Compliance of study subjects with use of CSII and CGM will be assessed by review of device downloads at each visit. Items assessed on downloaded reports will include percent time devices are used, number and timing of infusion set changes, bolus/basal delivery (as percentages of total daily insulin dose) and carbohydrate intake. Other significant subject assessments will include number of infusion set occlusions, and missed boluses. These assessments will be reviewed in both treatment arms via CGM and insulin pump downloads at each study visit.

#### **Other assessments: TRIM D**

TRIM D questionnaires will be completed at the beginning of the trial and at the end of each treatment period for the assessment of quality of life measures using each insulin.

### **STATISTICAL CONSIDERATIONS**

This is a 25-week prospective 2 arm crossover trial.

45 subjects with type 1 diabetes with good glycemic control who are experienced in the use of CSII (with any open loop pump) and CGM (Dexcom) will be randomized either to use Fiasp or NovoLog in CSII. CSII settings (basal, bolus, and correction factors) will be optimized for a 2-week run-in period followed by a 10-week period of CSII use with the assigned insulin. After a 10-week maintenance period, each group will cross over to the other insulin (NovoLog or Fiasp) by CSII for a second 2-week optimization period followed by a 10-week treatment period. Assuming a SD of 50 mg/dl for a well-controlled population of subjects with type 1 DM, a sample size of 45 subjects should be adequate to show a trend in the glycemic response time by CGM after an insulin bolus in this exploratory (pilot) study).

Subjects will be instructed to record from their personal Dexcom the pre-meal interstitial blood glucose (IBG) (for calculation of the correction insulin bolus). These values will be entered into the insulin pump at the time of initiation of the correction bolus as per standard practice. The postprandial IBG at the point when the titration arrow changes from 2-3mg/dL/min upward to 1 mg/dL/min (flat) or downward will be captured from the raw data report exported from Dexcom Clarity. The point at which the trend arrow changes will be referred to as the point of glucose plateau point (GPP). Severe hypoglycemic

385 events and their timing, in particular in relation to insulin boluses, will also be captured in the subject  
386 diary.

387 **Dependent Variables (recorded for each 12-week trial/insulin) repeated measures:**

388 Primary dependent variable:

389 The primary dependent variable is time for recovery from hyperglycemia (*defined earlier*) to premeal  
390 glucose target (*defined earlier*).

391 For each hyperglycemia event (Category 1 and 2) the date/time of start and the time for recovery will be  
392 recorded. Since these can both be determined by CGM downloads there should be no missing data.  
393 Depending on the extent of events observed, the number of events will be converted to a convenient  
394 ratio, e.g., events/week. For the times for recovery a mean will be computed. These variables will be  
395 computed separately for isolated correction boluses and correction boluses taken as part of a meal  
396 dose.

397  
398 Secondary dependent variables (recorded for the last 2 weeks of each 12-week trial/insulin):

- 399 1. Time to levelling off of a rising directional arrow (which signifies arrest of rising blood glucose =  
400 the glucose plateau point, or GPP) after each correction bolus. The date/time for each event and  
401 time will be recorded. For the number of events, a ratio will be computed. For the time to  
402 levelling off, a mean will be computed.  
403
- 404 2. Incidence of early post-correction hypoglycemia (*defined earlier*) within 60 minutes of use of  
405 correction bolus. The date/time for each event and time will be recorded. For the number of  
406 events, a ratio will be computed. For the time to levelling off, a mean will be computed.  
407
- 408 3. Incidence of early post-correction hypoglycemia (defined earlier) within 120 minutes of use of  
409 correction bolus. – Count incidences - nominal or ratio depending on range of values obtained.  
410 The date/time for each event and time will be recorded. For the number of events, a ratio will  
411 be computed. For the time to levelling off, a mean will be computed.  
412
- 413 4. Whether any modification in insulin sensitivity factor is required (for optimal correction dosing  
414 and hypoglycemia avoidance) when switching from conventional insulin aspart to Fiasp (i.e., will  
415 the sensitivity factor need to be increased when using Fiasp). For each patient this will be yes/no  
416 response. This value will be obtained during patient visits.  
417
- 418 5. TRIM-D scores will be obtained at the end of each 12-week period.  
419
- 420 6. To determine whether there is a late (3 to 4 hour) rise in BG as determined by CGM when using  
421 Fiasp as compared to conventional insulin aspart, and to see whether a change in insulin-on-  
422 board (IOB) factor for subsequent correction dosing will need to be modified (e.g, reduced from  
423 3 hours for aspart to 2 hours for Fiasp in patients with normal renal function). For the events  
424 recorded, a daily or weekly rate and a mean change will be computed.  
425
- 426 7. A GlycoMark value will be obtained at the end of each 12-week period.

8. An HbA1c value will be obtained at the end of each 12-week period.
9. Percent time spent in target range during each 12-week period.
10. Percent time spent in hyperglycemic range during each 12-week period.
11. Percent time spent in hypoglycemic range during each 12-week period.
12. Standard deviation of BG as determined by CGM for each 12-week period.

#### **Independent Explanatory Variable**

Whether the patient is using Fiasp or conventional insulin aspart for CSII and bolus injections when independent, control and dependent variable measures are obtained. Patients will be randomly assigned at the beginning of the study to one of the treatments for 12 weeks and then switch to the other treatment for the final 12 weeks.

#### **Other Explanatory Variables (recorded at visit 1):**

1. Gender of patient - nominal variable
2. Age of patient at start of study.
3. Time since diagnosis with Type 1 DM
4. First treatment – Fiasp or NovoLog

#### **Statistical Analysis**

All statistical analyses will be completed using R version 3.5.0 or higher.

A linear mixed-effects model with repeated measures will be used for the analysis. Specifically, the “lme” function provided in the nonlinear mixed effects models (nlme) package, authored by José Pinheiro and Douglas Bates, will be used.

#### **POWER CONSIDERATIONS**

To estimate power, the analysis was simulated under varying conditions.

#### **Simulation Assumptions:**

- Effect size: -20 minute reduction in time until stabilization following a correction bolus dose for the treatment group relative to the control group.
- Participants are assumed to have three correction bolus events per day. This determines the number of data points collected per person. While in reality the number of events will vary considerably by person and by day, this is believed to be a conservative estimate (i.e. participants will typically have more than three correction doses per day).
- Each patient will contribute 28 days worth of data. This corresponds to two two-week periods for each patient, with the first in the treatment arm and the second in the control arm or vice versa, depending on randomization.
- No changing of treatment assignment for patients within each arm.
- No dropout of patients. Dropout will not affect the ability to conduct the analysis or violate any modeling assumptions, but will reduce the study's power commensurate with the degree of data loss observed.
- No period effect. Times until stabilization are not expected to increase or decrease during the second phase of the cross-over trial due to fact that the first arm has already been conducted. Alternately, any effect of the first phase is expected to have washed out by the time of data collection during the second phase. Given the time between data collection periods in the two arms, the existence of a period effect seems unlikely.
- No time trend. On average, participants are not expected to increase or decrease their time until stabilization within each trial period (e.g. patients stabilize faster in response to a stabilization dose at the end of the data collection period during the first trial arm than they do at the beginning). Since data collection occurs during a relatively short window (two weeks) at the end of each period, this assumption is likely also easily met.
- Treatment arms are assumed to have an equal number of patients. This is not an assumption of the model, merely how the simulations were conducted. Consequently, sample sizes are considered in increments of 2. Minor violations of balance between groups after data collection can be expected to have a negligible impact on the results.

## Simulation Parameters

- The standard deviation of the random effect distribution, tau. Conceptually, each person has an innate average time until glucose stabilization following a correction bolus dose. Tau describes the variation of that distribution, indicating the distance between the participant with the fastest average time and the participant with the slowest average time. This distance between the average stabilization time for the fastest and slowest patient is evaluated at 1, 2, and 3, hours. Since the distribution is assumed to follow a normal distribution, for which the width of a 95% confidence interval is approximately 4 standard deviations, we evaluate values of tau = 15, 30, 45, corresponding to 60 min, 120 min, and 180 min divided by 4.
- The standard deviation of the error distribution, sigma. This parameter describes the random variation in time until stabilization for each participant about their own personal average. Where tau described the between-person variation in times, sigma describes the variation within each person's measurements. Sigma is assumed to equal 20 min, suggesting, by the same logic as for tau, that we expect most (95%) of the measurements for each person to fall within +/- 40min of their individual average values.

- The correlation between individual averages on control and treatment assignments,  $\rho$ . Where some participants can be expected to have average times until stabilization that are higher than the group average when assigned to the control group, it is reasonable to think that they will likewise have a higher average time than the group when assigned to the treatment group. A value of  $\rho = 1$  indicates perfect correlation between individual averages on treatment and control assignments, while a value of  $\rho = 0$  indicates no correlation. Both extreme values are considered. A value of  $\rho = 0$  is the more conservative estimate, however.

For each value of Tau (15, 30, 45), 2000 simulations, corresponding to 2000 randomly generated datasets, were performed. The simulation margin of error is  $\pm 0.026$ . With  $\rho = 0$ ,  $\tau = 30$ ,  $\sigma = 20$ , and the above assumptions, 80% power is achieved at approximately 23 subjects, while a power of 100% is achieved with a sample size of approximately 32 or greater. A value of 20 for sigma is based on previous studies (Russell-Jones, et al). If subjects bolus more than three times per day then power is increased. Further, smaller values of tau also increase power.

## **DATA HANDLING AND RECORD KEEPING**

The study data (CGM data and laboratory endpoints including HbA1c and GlycoMark) will be uploaded and stored in the cloud in HIPAA-compliant electronic files. Pertinent data for endpoint safety and efficacy analyses will be entered into and electronically filed in password-protected Excel spreadsheets. Hypoglycemia diaries will be on paper and stored as source documents along with paper CRF's capturing study-related procedures (history, physical exam, vital signs, con meds, AE's) at each visit. Patients will complete TRIM-D questionnaires, and responses will be tabulated into Excel spreadsheets for statistical analysis.

All paper source documents and CRFs will be stored on site. All electronic data will be stored in the cloud in HIPAA-compliant electronic files.

## **ETHICS**

The sponsor (Mountain Diabetes and Endocrine Center), its investigators and site staff will comply with all applicable regulatory and legal requirements, ICH GCP guidelines and the Declaration of Helsinki in obtaining and documenting the informed consent.

Informed consent will be obtained by a medically qualified site member (MD or RN) after each subject has had time to review the informed consent document and have any questions about the study answered. This is performed in a conference room at the study site in a private and unhurried fashion. The subjects may bring family members with them to witness the informed consent process. The informed consent documents will be paper documents that will be retained at the site, signed by the subject and investigator, and a copy will be provided to each subject.

Upon approval of the study protocol, the study will be submitted for approval to IntegReview IRB in Austin, Texas for review and approval. The informed consent document will include information about the IRB and contact information for the IRB, the site, and the study principal investigator.

The study will be conducted in accordance with ICH GCP guidelines and the Declaration of Helsinki.

545

**546 STUDY SCHEDULE**

547 Planned recruitment period: 48 weeks  
548 FPFV: Upon approval of sponsor and IRB approval (within 6 weeks of sponsor approval)  
549 LPLV: Within 52 weeks of FPFV  
550 Final study report: within 4 weeks of LPLV  
551 Manuscript submission of study results: within 12 weeks of study completion

552

553

**554 STUDY DRUGS AND MATERIALS**

555 Study medications: Fiasp, NovoLog (Novo Nordisk)  
556 Study CGM: Dexcom G5 or G6  
557 Insulin pumps: Medtronic MiniMed 523, 723, 630G & 670G (used in open loop “manual” mode),  
558 Tandem T-Slim and Omnipod  
559

**560 PACKAGING AND LABELLING OF STUDY MEDICATION**

561 Study insulin (conventional insulin aspart and insulin Fiasp) will be distributed at in-person study visits to  
562 each subject from the site. Conventional insulin aspart and Fiasp will be supplied in vials because all  
563 insulin will be administered via insulin pump. Subjects will use their own insulin pumps and pump  
564 supplies during the study. 1 Dexcom G6 sensor or 2 Dexcom G5 sensors, as applicable, will be provided  
565 by the site during the last 2 weeks of each treatment arm. All other Dexcom sensors will be supplied by  
566 the subjects. Dexcoms will be downloaded at each visit (see study visit flow sheet).

**567 STORAGE AND DRUG ACCOUNTABILITY OF STUDY MEDICATION**

568 Study insulins will be received in temperature-controlled containers and the temperature of the  
569 medication upon receipt will be recorded. Study insulins will be stored at the study site in refrigerators  
570 maintained between 2 and 8 degrees Celsius; the temperature will be monitored and recorded daily.  
571 Fiasp vials will not be stored in or near a freezing compartment, and will not be exposed to excessive  
572 heat or light and will never be frozen. No trial medication will be dispensed to any individual not  
573 enrolled in the study. All medication used in the study will be recorded in the CRF at each study  
574 dispensing visit. Subjects will be provided with sufficient study insulin for study completion.

**575 AUXILIARY SUPPLY**

576 Subjects will use their own insulin pumps, pump supplies, and Dexcom CGM/sensors, except for Dexcom  
577 G5 or G6 sensor(s) provided during the last 2 weeks of each treatment arm.

**578 RANDOMIZATION AND BLINDING**

579 This is an open-label crossover trial. Subjects will be randomized to treatment sequence (Fiasp then  
580 NovoLog or NovoLog then Fiasp), each for a 12-week treatment period, by CSII. Randomization  
581 sequence will be determined by computerized randomization program. All patients will receive both

582 treatments unless they drop out. Dropouts are unlikely since the participants are all regular continuing  
 583 patients of the site's clinical practice.  
 584

## 585 **CONCOMITANT ILLNESSES AND MEDICATIONS**

### 586 **Definitions:**

587 Concomitant illness: any illness that is present at the start of the trial (at the first study visit).  
 588 Concomitant medication: any medication other than the trial product(s) that is taken during the trial,  
 589 including the screening and run-in periods.  
 590 Details of all concomitant illnesses and medication will be recorded at trial entry (at the first study visit).  
 591 Any changes in concomitant medication will be recorded at each visit.  
 592 The information collected for each concomitant medication will include start date, stop date or  
 593 continuing, and indication.  
 594 For each concomitant illness, date of onset, date of resolution or continuing, will be recorded.  
 595

## 596 **ADVERSE EVENTS**

597 Adverse events will be captured at each study visit and recorded on CRF's. Special AE and SAE reporting  
 598 forms have been created to capture these events. SAE's will be reported within 24 hours of discovery to  
 599 appropriate local and federal authorities as well as to the IRB when appropriate. The study site will  
 600 comply with all local legal, regulatory, and IntegReview IRB requirements. In addition, any other events  
 601 that have been submitted to the health authorities according to local regulatory requirements will be  
 602 sent to Novo Nordisk at time of submission to health authorities, at the latest.

603 Mountain Diabetes and Endocrine Center, its investigators, and site staff will be responsible for  
 604 reporting of all adverse events including serious adverse events (SAE), and serious adverse drug  
 605 reactions (SADRs) to the competent authority and independent ethics committee/institutional review  
 606 board based upon federal regulations and local/IRB policies.

607 Mountain Diabetes and Endocrine Center, its investigators, and site staff will report to Novo Nordisk all  
 608 SAEs, and SADRs at the same time such events are reported to regulatory authorities or within 15 days  
 609 from the site becoming aware of such adverse events, whichever comes first.

610 Mountain Diabetes and Endocrine Center, its investigators, and site staff will collect the following  
 611 information at minimum for each of these events:

- 612 1. Study name
- 613 2. Patient identification
- 614 3. Event (with appropriate diagnosis)
- 615 4. Drug
- 616 5. Reporter identification
- 617 Also 6) Causality, and 7) Outcome might be reported, if appropriate.

618

## 619 **DEFINITIONS**

### **Adverse Event (AE):**

An AE is any undesirable medical event occurring to a subject in a clinical trial, whether or not related to the trial product(s). This includes events reported from the first trial related activity after the subject has signed the informed consent and until post treatment follow-up period as defined in the protocol. The following will not be recorded as AEs, if recorded as medical history/concomitant illness on the CRF at screening:

- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial related activity after the subject has signed the informed consent
- Pre-existing conditions found as a result of screening procedures

### **Clinical Laboratory Adverse Event:**

A clinical laboratory AE is any clinical laboratory abnormality regarded as clinically significant, i.e. an abnormality that suggests a disease and/or organ toxicity and is of a severity which requires active management, (i.e. change of dose, discontinuation of trial product, more frequent follow-up or diagnostic investigation).

### **Serious Adverse Event (SAE):**

A serious AE is an event that results in any of the following:

- Death
- A life-threatening\* experience
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening\*, or require hospitalization may be considered an SAE when, based upon appropriate medical judgement, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

\*The term life-threatening in the definition of SAE refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.

### **Serious Adverse Drug Reaction (SADR):**

An adverse drug reaction (ADR) is an adverse event for which a causal relationship (Possible/Probable relation) between the study drug and the occurrence of the event is suspected. The ADR will be classified as **serious** if it meets one or more of the seriousness criteria.

**Medical Events of Special Interest (MESI):** A MESI is (1) a medication error (e.g. wrong drug administration or wrong route of administration) or (2) a suspected transmission of an infectious agent via the product

### **Non-Serious Adverse Event:**

A non-serious AE is any AE which does not fulfil the definition of an SAE.

### **Severity Assessment Definitions:**

- Mild: Transient symptoms, no interference with the subject's daily activities



- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

#### **The Glucose Plateau Point (GPP):**

The point of arrest on the Dexcom CGM when the glucose trend arrow changes from upwards to horizontal after each correction bolus and/or meal bolus with insulin.

#### **Relationship to study medication Assessment Definitions:**

- Probable: Good reason and sufficient documentation to assume a causal relationship
- Possible: A causal relationship is conceivable and cannot be dismissed
- Unlikely: The event is most likely related to an etiology other than the trial product

#### **Outcome Categories and Definitions:**

- Recovered: Fully recovered or by medical or surgical treatment the condition has returned to the level observed at the first trial related activity after the subject signed the informed consent
- Recovering: The condition is improving, and the subject is expected to recover from the event. This term should only be used when the subject has completed the trial
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralysed). Any AE recovered with sequelae will be rated as an SAE
- Not recovered
- Fatal
- Unknown

#### **Collection, Recording and Reporting of Adverse Events**

All events meeting the definition of an adverse event will be collected and reported from the first trial-related activity after the subject has signed the informed consent and until the end of the post-treatment follow-up period as stated in the protocol.

#### **Follow-up of Adverse Events**

**During and following a subject's participation in this clinical trial, Mountain Diabetes and Endocrine Center, its investigators and site staff, will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.**

**All adverse events classified as serious or severe or possibly/probably related to the trial product will be followed until the subject has recovered and all queries have been resolved.** For cases of chronic conditions, follow-up until the outcome category is "recovered" is not required, as these cases can be closed with an outcome of "recovering" or "not recovered".

All other adverse events will be followed until the outcome of the event is "recovering" (for chronic conditions), or "recovered" or until the end of the post-treatment follow-up stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved.

## **Pregnancy**

Study subjects will be instructed to notify the site and study physician immediately if they become pregnant.

**Mountain Diabetes and Endocrine Center, its investigators and site staff, will report to Novo Nordisk any pregnancy occurring during the trial period. Reporting of pregnancy by the site will occur within the same timelines described above for reporting of Adverse Events.**

Pregnancy complications will be recorded as adverse event(s). If the infant has a congenital anomaly/birth defect this must be reported and followed up as a serious adverse event.

## **Precautions/ Insulin Over-dosage**

Study subjects will be prescribed glucagon kits and treatment of hypoglycemia will be reviewed with subjects upon enrolment into the study.

## **LIABILITY AND SUBJECT INSURANCE**

**During and following a subject's participation in trial, Mountain Diabetes and Endocrine Center and the study physicians will provide adequate medical care to the study subject for any study-related adverse events, including clinically significant laboratory values related to the study. This medical care for study subjects will be provided regardless of their insurance status.**

**Mountain Diabetes and Endocrine Center and its investigators will be responsible for the conduct of the study and agree to defend, indemnify, and hold harmless Novo Nordisk, any of its parent companies, affiliates, or subsidiaries, and their respective officers, directors, employees, agents, representatives, distributors, salespersons, customers, licensees, and end-users from and against any claim, suit, demand, loss, damage, expense or liability imposed by any third party arising from or related to: (a) any breach of sponsor-investigator's obligations or representations; or (b) sponsor-investigator's negligent or grossly negligent use or willful misuse of the study drug, the results, or services derived therefrom. This indemnification shall not apply in the event and to the extent that a court of competent jurisdiction or a duly appointed arbiter determines that such losses or liability arose as a result of Novo Nordisk's gross negligence, intentional misconduct, or material breach of its responsibilities.**

## **EVALUABILITY OF SUBJECTS**

Only the principal investigator has the authority to exclude any subjects or data observations after the initiation of the study, initial selection of subjects, and beginning of data collection. Possible reasons for such actions might be (1) questionable validity or reliability of data collection or measurement techniques for a particular subject, (2) misrepresentation of initial selection criteria by a subject, or (3) changes in the health conditions of subjects that might affect the reliability or validity of measurements or accuracy of data collection procedures. The reasons for any such action will be carefully documented by the principal investigator and kept on file for the actionable subject.

## **PREMATURE TERMINATION OF STUDY**

The study will only be discontinued prematurely in the unlikely event of an unforeseen safety concern arising from the study protocol.

## **PUBLICATION PLAN**

Within 12 weeks of study completion and data analysis, the results of this study (which will be registered with [clinicaltrials.gov](https://clinicaltrials.gov)) will be submitted in abstract form for oral or poster presentation at a diabetes conference (either ADA or EASD) and a manuscript of the complete study results will be submitted to a peer-reviewed journal focused on clinical diabetes for publication.

## **REFERENCES**

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Trial Procedures	Screening	Treatment Period 1 (First Treatment Group)						Treatment Period 2 (Second Treatment Group)						
Visit (V), Phone (P)	V1	V2 (Randomization)	V3	PV4	V5	PV6	PV7	V8 (Crossover)	V9	PV10	V11	PV12	PV13	V14 (EOT)
Timing of Visit (Weeks)	-1	0	2	4	6	8	10	12	14	16	18	20	22	24
Visit Window (Days)	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Informed Consent	X													
In/Exclusion Criteria	X	X												
Demography & Tobacco Use	X													
Physical Examination		X						X						X
Concomitant Illness /Medical History	X													
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Child Bearing Potential	X													
Pregnancy Test, Urine	X							X						X
Height	X													
Body Weight	X	X	X		X			X	X		X			X
Vital Signs	X	X	X		X			X	X		X			X
CGM Download	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense Dexcom Sensor(s)					X						X			
Insulin Pump Download	X	X	X		X			X	X		X			X
Insulin Optimization	X	X	X					X	X					
Meal Challenge		X						X						
BLOOD SAMPLING														
HbA1c (central laboratory)	X							X						X

GlycoMark	X							X						X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemia Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Technical Complaints		X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion Site Reactions	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infusion Site Occlusions	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X												
Dispensing of Trial Product		X	X		X			X	X		X			
Drug Accountability			X		X			X	X		X			X
Treatment Crossover								X						
Questionnaires/Surveys		X						X						X
<b>REMINDERS</b>														
Insulin Instruction		X						X						X
Dispense Diary	X	X	X		X			X	X		X			
Collect Diary		X	X		X			X	X		X			X
Review Diary		X	X	X	X	X	X	X	X	X	X	X	X	X
Confirmation of Consumption of 3 Meals Daily	X	X	X	X	X	X	X	X	X	X	X	X	X	
Fasting Visit		X						X						
Instruction on Dexcom Bolus Entry						X	X					X	X	
CRC Data Collection and Data Validation								X						X